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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| SNYDER, STUART | |
| ART UNIT | PAPER NUMBER |
| 1648 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/578,976 | HSU ET AL. | |
| | Examiner | Art Unit | |
| | STUART W. SNYDER | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,6,8-23 and 25-33* is/are pending in the application.

4a) Of the above claim(s) *6,8-23 and 25-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3* is/are rejected.

7)☒ Claim(s) *26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 May 0206* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1 and 3 in the reply filed on 12/2/2009 is acknowledged. Claims 1 and 3 are initially examined in view of Applicants' further election of *Salmonella sp*. as Applicants correctly interpreted the Examiner's species election requirement in the Office Action mailed 10/16/2008.

   Claims 1, 3, 6, 8-23, 25-26, and 28-34 are pending. Claims 6, 8-23, 25-26 and 28-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

   Please note that the claims have been renumbered per section 2 below and all claim numbering in the instant Office Action refer to renumbered claims.

### *Claim Objections*

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

   Misnumbered claims 26-34 have been renumbered 27-35.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Waring (JBC, 1990). The claim is drawn to a method for identifying an agent that reduces apoptosis of a macrophage cell comprising contacting a macrophage cell with a test agent and detecting reduced RNA-dependent Protein Kinase (PKR) activity compared to control macrophage PKR activity.

Waring teaches a method of inducing apoptosis in murine macrophages and studying modulation of apoptosis. One method Waring used to study apoptosis in murine macrophages is to incubate apoptotic inducers, such as gliotoxin derived from fungi, with macrophages in the presence or absence of test agents; in the case of the 1990 publication Waring used protein synthesis inhibitors such as cycloheximide to determine if the apoptotic pathway induced by gliotoxins involved protein synthesis. To quantify the apoptotic effect of gliotoxin and potential inhibition by test agents, Waring measured DNA fragmentation (see, especially Figures 1 and 2), methods taught by Applicant as being sufficient to measure PKR-induced apoptosis. Thus, gliotoxin induces apoptosis via a PKR-dependent pathway and Waring teaches a method to test apoptosis inhibitors in macrophages by measuring PKR activity in test cells compared to control cells.

The conclusion that gliotoxin-induced apoptosis necessarily involves PKR is buttressed by the facts that gliotoxin *per se* generates stressful oxidative species (peroxides) and oxidative-stressed murine monocytes apoptose at least via the PKR pathway.

Thus, each and every limitation of claim 1 is taught by Waring and the claim is properly rejected under 35 USC § 102.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waring, Jesenberger, *et al.* (J. Expt. Med., 2000), and Liu, *et al.* (J. Virol., 2001).

The limitations of claim 1 is summarized above (see section 3); claim 3 adds the additional step of further characterizing the agent as an anti-bacterial agent to the method of identifying an agent for reducing apoptosis in macrophages. The teachings of Waring are summarized above (see section 3); Waring does not teach identification of apoptosis inhibitors as antibiotics.

Jesenberger, *et al.* teaches a method of induction of apoptosis in macrophages using pathogenic *Salmonella typhimurium* strains that induce apoptosis in murine macrophages via Caspase 2 pathway and a specific inhibitor of that pathway, Z-VDVADfmk, which lessens the pathogenic nature of the bacteria (see p. 1036,

Materials and Methods; p. 1042, Results, "*Caspase-2 Inhibition Delays Apoptosis in Both wt and Caspase-1–deficient Macrophages*") by delaying the onset of apoptosis. The involvement of microbial and non-microbial proapoptotic entities in Caspase-dependent PKR mediated apoptosis was well known in the microbial arts as evidenced by Liu, *et al.* (see, p 6407-8, Discussion).

An artisan of ordinary skill in the microbiological arts would have found it obvious to combine the teachings of Waring, Jesenberger, *et al.* and Liu, *et al.* to arrive a method to identify inhibitors of apoptosis in macrophages as a result of Salmonella infection that also may function as antibiotics. The artisan would have been motivated to combine the three methods because of the artisan's knowledge of that multiple causes of apoptosis, especially including viral, chemical, and bacterial causes, proceed through a PKR pathway as taught by Liu, *et al.*, and that Caspase 2 is necessarily involved in Toll-like receptor mediated apoptosis as taught by Jesenberger, *et al.* Jesenberger, et al. further suggests that Caspase 2 inhibitors may be of importance as antibiotics:

> The rapid induction of macrophage apoptosis may be instrumental in establishing/maintaining systemic infection, and if so, it may **represent an attractive therapeutic target**. However, general caspase inhibitors may interfere with T cell function (45, 46), and caspase-1–specific inhibitors might prevent the production of cytokines, which play an important role in the host resistance to infection (55). Understanding the alignment of the apoptotic pathways initiated by Salmonella might prove **important for the design of**

**therapeutic protocols that reduce macrophage apoptosis** without altering the inflammatory response of the host.

The skilled artisan would have a reasonable expectation of success in combining the methods because both Jesenberger, *et al.* and Liu, *et al.* teach inhibition of apoptosis *per se* functions as an antibiotic or antiviral in microbe infected macrophages and that each of these pathogens possess mechanisms to evade host innate immune responses of macrophages. Thus, the invention as a whole is prima facie obvious in view of Waring, Jesenberger, *et al.* and Liu, *et al.*

***Conclusion***

5. No claims are allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STUART W. SNYDER whose telephone number is (571)272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher/
Primary Examiner, Art Unit 1648

Stuart W Snyder
Examiner
Art Unit 1648

sws